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Review

The dual face of connexin-based astroglial Ca^{2+} communication: A key player in brain physiology and a prime target in pathology ☆

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ABSTRACT

For decades, studies have been focusing on the neuronal abnormalities that accompany neurodegenerative disorders. Yet, glial cells are emerging as important players in numerous neurological diseases. Astrocytes, the main type of glia in the central nervous system , form extensive networks that physically and functionally connect neuronal synapses with cerebral blood vessels. Normal brain functioning strictly depends on highly specialized cellular cross-talk between these different partners to which Ca^{2+}, as a signaling ion, largely contributes. Altered intracellular Ca^{2+} levels are associated with neurodegenerative disorders and play a crucial role in the glial responses to injury. Intracellular Ca^{2+} increases in single astrocytes can be propagated toward neighboring cells as intercellular Ca^{2+} waves, thereby recruiting a larger group of cells. Intercellular Ca^{2+} wave propagation depends on two, parallel, connexin (Cx) channel-based mechanisms: *i*) the diffusion of inositol 1,4,5-trisphosphate through gap junction channels that directly connect the cytoplasm of neighboring cells, and *ii*) the release of paracrine messengers such as glutamate and ATP through hemichannels ('half of a gap junction channel'). This review gives an overview of the current knowledge on Cx-mediated Ca^{2+} communication among astrocytes as well as between astrocytes and other brain cell types in physiology and pathology, with a focus on the processes of neurodegeneration and reactive gliosis. Research on Cx-mediated astroglial Ca^{2+} communication may ultimately shed light on the development of targeted therapies for neurodegenerative disorders in which astrocytes participate. This article is part of a Special Issue entitled: Calcium signaling in health and disease. Guest Editors: Geert Bultynck, Jacques Haiech, Claus W. Heizmann, Joachim Krebs, and Marc Moreau.

1. Introduction

In the brain, multiple billions of cells communicate with one another in order to process highly complex information. While a major part of the intercellular communication occurs via neuronal synapses, glial cells encompassing astrocytes, oligodendrocytes, tanycytes, radial glia and microglia, are critically involved in shaping cell-to-cell communication in the central nervous system (CNS) [1]. Cell–cell communication occurs between neurons, astrocytes, oligodendrocytes, activated microglia, vascular cells and ependymal cells [2] and is in large part

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AQP4, aquaporin 4; APP, amyloid precursor protein; BAPTA, 1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid; BBB, blood–brain barrier; $[Ca^{2+}]_e$, extracellular Ca^{2+} concentration; $[Ca^{2+}]_i$, cytoplasmic Ca^{2+} concentration; cADPR, cyclic adenosine diphosphoribose; CNS, central nervous system; CRACs, Ca^{2+} release activated channels; CSD, cortical spreading depression; Cx, connexin; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmic reticulum; GFAP, glial fibrillary acidic protein; GJ, gap junction; GJIC, gap junction-mediated intercellular coupling; GPCR, G-protein-coupled receptor; HC, hemichannel; IICR, inositol 1,4,5-trisphosphate-induced Ca^{2+} release; ICW, intercellular Ca^{2+} wave; IL-1β, interleukin-1β; IP_3, inositol 1,4,5-trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor; $[K^+]_e$, extracellular K^+ concentration; KO, knock-out; L-AAA, L-alpha-aminoadipic acid; LPS, lipopolysaccharide; MAM, mitochondria-associated endoplasmic reticulum membrane; MCU, mitochondrial Ca^{2+} uniporter; GluR, glutamate receptor; MW, molecular weight; NAD+, nicotinamide adenine dinucleotide; NCX, Na^+/Ca^{2+} exchanger; NFAT, nuclear factor of activated T-cells; NFTs, neurofibrillary tangles; NGVU, neuro-glio-vascular unit; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; Panx, Pannexin; PLC, phospholipase C; PGE_2, prostaglandin E_2; PS, presenilins; PDS, paroxysomal depolarization shift; PTP, permeability transition pore; ROS, reactive oxygen species; RyR, ryanodine receptor; SMC, smooth muscle cell; SOCE, store-operated Ca^{2+} entry; TNF-α, tumor necrosis factor-α; TRP channel, transient receptor potential channel; VDAC, voltage-dependent anion channel

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mediated by paracrine signaling, involving the release, diffusion and interaction of a messenger molecule with its receptor. Additionally, more direct signaling is possible by the exchange of ions and low molecular weight (MW) molecules (<1.5 kDa) via gap junctions (GJs) that cluster in plaques and directly connect the cytoplasm of neighboring cells. GJs are formed by the docking of two hemichannels (HCs). The plasma membrane normally also contains HCs *not* incorporated into GJs which are sometimes referred to as unapposed HCs. These HCs are commonly closed but may be activated in response to various stimuli, thereby opening a pore that allows ionic and molecular exchange between the intra- and extracellular environment. Opening of unapposed HCs is a potential pathway for the diffusive release of messenger molecules like ATP and glutamate and may therefore contribute to paracrine signaling [3]. GJs and HCs are composed of connexin (Cx) subunits arranged in a, respectively dodecameric or hexameric, configuration. Cxs are tetraspan membrane proteins of which 21 human species have been identified and named according to their MW. Pannexins (Panxs) are another family of channel-forming proteins that have topological similarity to Cx hemichannels. Currently, three human Panxs (Panx1–3) have been identified. Both Cx43 and Panx1 are predominant in the CNS (Table 1) [4–8].

Normal brain functioning strictly depends on highly specialized cellular cross-talk to which calcium ions (Ca^{2+}) largely contribute as a second messenger. In the brain, Cx/Panx channels crucially contribute to the cell-to-cell propagation of increases in the cytoplasmic free Ca^{2+} concentration ($[Ca^{2+}]_i$), known as intercellular Ca^{2+} waves (ICWs) [9–11]. Neuronal communication primarily relies on action potential firing whereby $[Ca^{2+}]_i$ changes have a critical role in regulating neurotransmitter release, synaptic plasticity and gene expression [12–14]. For electrically non-excitable cells such as glia and vascular endothelial cells, Ca^{2+} signals are the major fast (on a second time scale) system available for intra- as well as intercellular signaling. ICWs typically emerge in glial networks [11,15] as has been demonstrated in vivo [16–19], bringing up the question whether these ICWs play an active role in normal brain functioning and information processing, particularly at the level of synaptic signaling and regulation of blood supply. In addition, a wide diversity of pathologies (e.g. brain ischemia [20], Alzheimer's disease (AD) [21,22], CNS traumatic injury [23,24] and epilepsy [25,26]) has been associated with abnormal intercellular Ca^{2+} signaling, which is linked to inflammatory conditions and unwarranted cell death, supporting a pathological function for ICWs. In this review, we discuss the currently available evidence that describes Ca^{2+} signaling in the brain, focusing on intra- and intercellular glial Ca^{2+} signaling and the contribution of Cx channels, both in physiology and pathology.

2. The neuro-glio-vascular unit

The term 'neurovascular unit' originally emerged as a concept to widen the scope of possibilities for therapeutic interventions in stroke (Report of the Stroke Progress Research Group, 2002, www.ninds.nih.gov) and has been instrumental in scaling down the classical neurocentric view in favor of a more integrated approach by including vascular and blood targets. We indulge in denoting this unit as the 'neuro-*glio*-vascular unit' (NGVU) to underscore the importance of glial cells as central players linking neurons to the cerebral vasculature. The NGVU is composed of neurons, astrocytes, microglial cells, endothelial cells, pericytes, smooth muscle cells (SMCs) and circulating blood cells [27] (Fig. 1). Functionally, these cells interact to control synaptic communication, blood–brain barrier (BBB) function, local blood supply, neuronal development and surveillance/immune function [28].

Table 1
Main connexin and pannexin species expressed in the neurogliovascular unit.

	Connexin	Pannexin
Astrocyte	Cx26, Cx30, Cx43	Panx1, Panx2[a]
Microglia	Cx32, Cx36, Cx43[b]	Panx1
Oligodendrocyte	Cx29, Cx32, Cx47	Panx1, Panx2
Neuron	Cx30.2, Cx31.1, Cx36, Cx40, Cx45	Panx1, Panx2
Endothelial cell	Cx37, Cx40, Cx43	ND
Pericyte	Cx37, Cx40, Cx43	ND

[a] De novo expression in reactive hippocampal astrocytes subjected to ischemia/reperfusion injury.
[b] Expressed in activated microglia, not in resting microglia.

Astrocytes are centrally positioned within the NGVU, where they form extensive networks that physically and functionally connect neuronal synapses with cerebral vessels [2]. At one end, astrocytes send their processes to neuronal synapses, where they join pre- and postsynaptic structures, altogether forming a 'tripartite synapse'. A single rodent astrocyte may contact an estimated 140,000 synapses while in the human brain, astrocytes are hypothesized to support and modulate the function of roughly two million synapses [29,30]. By surrounding the synaptic cleft, astrocytes sense neuronal signaling activities and modulate them by secreting gliotransmitters like ATP, glutamate, D-serine and adenosine [31–36]. At the other end, astrocytes project 'endfeet' onto brain capillary endothelial cells and pericytes, thereby enwrapping 98% of the vascular surface area. At the synaptic as well as vascular contact points, astrocytes are additionally equipped with a large repertoire of neurotransmitter receptors [37] that sense synaptic, neurometabolic and vascular activities. The dual contact with neurons and cerebral vessels thus provides astrocytes with the unique architectural advantage for sensing neuronal activity, integrating electrochemical information and exchanging this information with the vasculature, for example, by releasing vasoactive substances such as nitric oxide (NO), prostacyclins, epoxyeicosatrienoic acids, glutamate, adenosine and ATP [38–40]. As such, the NGVU performs a homeostatic control over the neuronal milieu, which is required for proper functioning of neurons and their synapses.

3. Connexin signaling and glial network communication

Twelve Cxs and two Panxs have been identified in the various CNS cell types (Table 1). Each cell type expresses a unique combination of Cx species that typically depends on the brain region and on the developmental stage, with Cx43 being most ubiquitously expressed [6–8,41–43]. It is predominant in astrocytes, activated microglia, developing neurons, SMCs, endothelial cells and pericytes. Cx-mediated intercellular communication, being a typical feature of glial cells, is thought to play an important role in signal transmission at the NGVU, primarily via the formation of glial networks [44].

Astroglial cells prominently express Cxs and through extensive gap junctional coupling they establish astrocytic networks that support long-range communication and transport [44]. Importantly, interastroglial coupling is not uniform but endowed with anatomical or functional specificity, and is subject to modulation [45,46]. Cx43 and Cx30 are the main Cx species expressed in astrocytes and both contribute to GJ-mediated intercellular coupling (GJIC) between these cells [47–52]. Cx43 and Cx30 are primarily expressed in astrocytic processes that surround the synaptic cleft, but are also enriched in astrocytic endfeet. As GJs, these Cxs support intercellular trafficking of ions and small signaling molecules through perivascular and perisynaptic astroglial networks. Recent data obtained from transgenic mice with a targeted deletion of Cx26 in neuronal and glial cells, provided unequivocal evidence for the additional presence of Cx26 in astrocytic GJ plaques as well as for heterotypic plaques formed between astrocytes and oligodendrocytes [53]. Other Cxs (Cx40 and Cx45) have been detected in astrocytes, but are expressed at low levels [54,55]. The pattern of Cx expression in astrocytes is subject to alterations; e.g., Cx30 and Cx43 are upregulated in the presence of synaptically active neurons [51,56] and astrocyte-specific Cx43 knock-out (KO) is associated with a compensatory increase in Cx30 expression [57]. Under pathological conditions, Cx

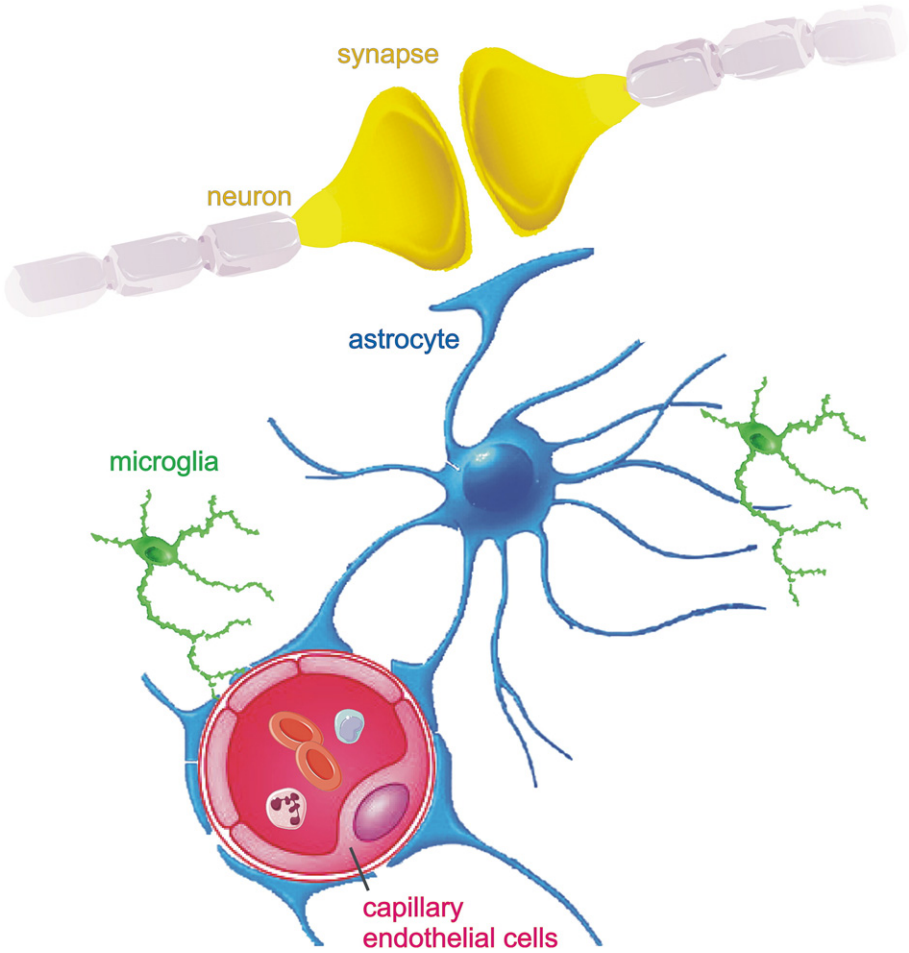

Fig. 1. Schematic diagram of the neurogliovascular unit. Astrocytes send projections towards the synapse, where they form the tripartite synapse together with pre-and postsynaptic nerve terminals. At the other end, astrocyte endfeet enwrap the vascular wall from the capillary to the arteriolar level. It this way, neurons can influence the endothelium, using the astrocytes as intermediate players.

expression may additionally experience marked changes (see Section 5).

Several global and conditional Cx KO mice for the glial Cxs (Cx43, Cx30 and Cx26) are available and, as a consequence of the previously mentioned compensatory changes in the expression levels of other Cxs, KO mice deficient for multiple glial Cxs have been generated as well [45]. Targeted astrocytic ablation of Cx43 on a global Cx30 KO background renders mice that are largely devoid of astrocytic GJIC. The diffusion of glucose metabolites through the astrocytic network was abolished in hippocampal slices from these double KO mice [49]. Astrocytic networks exert homeostatic control over the composition of the extracellular environment, thereby influencing neuronal function and survival. Astrocytic GJIC is crucial for the supply and delivery of energy molecules and for the removal and spatial buffering of extracellular K^+ and glutamate [2,52]. Increased neuronal activity augments astrocytic GJIC [49,58] and induces vasodilation of upstream pial arterioles. While in most perfusion beds, upstream signaling from capillaries to arterioles is mediated by the communication of electrical signals via endothelial GJs, there seems to be an alternative pathway in the brain consisting of the propagation of Ca^{2+} signals over astrocytic endfeet that strongly express Cx43 [59]. Work with Cx30/Cx43 double KO animals has additionally provided evidence that these Cxs are necessary for normal BBB integrity and function [48]. The evidence above strongly suggests that energy delivery, clearing and signaling functions of astroglial Cx channels are adapted to the level of neuronal activity. At the neuronal and vascular contact points, transport and signaling interactions with the glial network are mainly governed by mechanisms other than GJs [50,60] although direct signaling through neuron–glial or endothelial–glial GJs has been reported in cell culture systems [61–64]. By means of immunolabeling techniques or functional assays, GJs between astrocytes and neurons have been detected in brain slices [65–67]. GJs between astrocytes and endothelial cells have been described in cell culture models [68] but they are normally not present at the healthy astrocyte–endothelial interface, presumably because of the presence of a continuous basal membrane. However, this does not exclude the possibility that heterocellular astrocyte–endothelial GJs can form under pathological conditions.

The participation of GJs in brain functioning has been abundantly reviewed but evidence for contribution of astrocytic HCs has only been accumulating over the past 10 years [69,70]. Before being incorporated into GJs, HCs form a bidirectional diffusion pathway for ions, small signaling molecules and energy substrates [3,69,71]. In this respect, Cx43 HCs have been demonstrated, mostly under in vitro conditions, to function as a release pathway for molecules such as ATP, glutamate, prostaglandin E_2 (PGE_2), nicotinamide adenine dinucleotide (NAD^+) and inositol 1,4,5-trisphosphate (IP_3) [72–77]. Cx43 HC opening has also been proposed to act as a pathway for the uptake of energy molecules in astrocytes in response to pro-inflammatory cytokines [78]. However, the biological significance of HCs is still a matter of debate as it is hard to understand how a poorly selective plasma membrane channel, with a conductance about twice the conductance of the corresponding GJ channel [79,80], can contribute to the normal functioning of a cell [81]. It was therefore hypothesized that HCs remain closed under most conditions to prevent leakage of metabolites and nutrients

and loss or entry of ions that would otherwise lead to cell dysfunction and cell death. Under resting conditions, Cx43 HCs exhibit a low open probability in cultured cells [79,82] that can be increased by exposure to various stimuli such as mechanical stimulation, changes in phosphorylation status [83], ischemic conditions [84], pro-inflammatory cytokines [78], oxidative stress [85], and an increase in $[Ca^{2+}]_i$ [86] or decrease in extracellular Ca^{2+} concentration ($[Ca^{2+}]_e$) [87]. Although most of these stimuli are associated with cellular stress, HC function has been associated with various aspects of the cellular life cycle, including cell proliferation, as well as with the normal functioning of various cell types [88]. Their involvement under normal non-pathological conditions is now supported by the observation that $[Ca^{2+}]_i$ changes, in the physiological (submicromolar) range, trigger HC opening [86,89]. HC activity has also been recorded in cells exposed to endogenous ligands associated with cell proliferation and differentiation [83,90,91]. Nerve growth factor stimulated neurite outgrowth in PC12 cells was for instance mediated by HCs through ATP release [90]. Recently, Stehberg and co-workers pinpointed a contribution of astroglial Cx43 HCs in the basolateral amygdala to the consodilation of fear memory [92], suggesting a role of these channels in gliotransmitter release. Of note, functional Panx1 HCs have also been reported in astrocytes, but their role as gliotransmitter release channels has been less characterized and they do not form GJs between cultured astrocytes [93–95]. Hence, these channels are further referred to as Panx channels instead of Panx HCs [96].

Besides forming channels, Cxs also exert non-channel signaling functions [97,98]. Growing evidence suggests that Cx proteins directly control gene expression. Cx gene transfection is indeed known to affect the expression of genes encoding for growth-, differentiation- and cell death-modulating proteins [98]. The up- or down-regulation of various genes with diverse functions in the brain of Cx43-null mice indicate that Cxs regulate multiple cellular processes [99,100]. Irrespective of their channel-forming capacity, Cxs modulate P2Y receptor signaling [101,102] and cytoskeletal proteins in astrocytes [103]. Recently, Cxs were found to be crucial for glial-guided neuronal migration without acting in the classical channel-mediated manner [104,105]. Instead, Cx26 and Cx43 GJs, expressed at the contact points between radial fibers and migrating neurons, provided dynamic adhesive contacts that interact with the internal cytoskeleton to enable leading process stabilization along radial fibers as well as the subsequent translocation of the nucleus [104].

4. Ca^{2+} signaling in the healthy brain

4.1. General concepts of intra- and intercellular Ca^{2+} signaling

$[Ca^{2+}]_i$ is regulated through a strongly organized interplay between Ca^{2+} entry from the extracellular space, Ca^{2+} release from intracellular storage sites, and Ca^{2+} extrusion out of the cells or its sequestration back into the stores. Most cytoplasmic Ca^{2+} is furthermore bound by Ca^{2+} buffering proteins such as parvalbumin, calretinin and calbindin [106]. As a result, $[Ca^{2+}]_i$ in resting brain cells varies between 80 nM and 100 nM [21,107]. At high cytosolic levels, Ca^{2+} ions have a deleterious action; they cause aggregation of proteins and nucleic acids, affect the integrity of lipid membranes and initiate the precipitation of phosphates, and are thus incompatible with life [108]. Therefore, all living cells keep $[Ca^{2+}]_i$ at low nanomolar levels, creating a steep concentration gradient between the extracellular environment (~1 mM [109–111]), the cytoplasm and the Ca^{2+} store content. Free cytoplasmic Ca^{2+} represents only a small part of the total cellular Ca^{2+} as most of the intracellular Ca^{2+} is sequestered in intracellular stores to prevent the toxic effects of a high $[Ca^{2+}]_i$. The endoplasmic reticulum (ER) is considered the predominant Ca^{2+} store as it contains approximately 70% of the cell's total Ca^{2+} reserve, corresponding to Ca^{2+} concentrations up to 0.5 mM [112–114]. Additionally, mitochondria play an important role in the Ca^{2+} household of cells [115]. Transport across the plasma membrane and membranes of the intracellular compartments is governed by a family of Ca^{2+} channels and transporters that are based on the diffusion of Ca^{2+} down its concentration gradient (passive downhill), causing an increase in $[Ca^{2+}]_i$. The clearance of cytosolic Ca^{2+} depends on different energy-dependent transport mechanisms that act against the concentration gradient (active uphill) (Table 2) [116].

Variations in $[Ca^{2+}]_i$ control a multitude of biological processes over a wide dynamic range including cell proliferation, differentiation, neurotransmitter release, secretion, synaptic plasticity, gene expression, immune responses, muscle contraction, endothelial permeability, apoptosis and many others [106]. To ensure specificity, Ca^{2+} signals are highly organized in time and space [10]. Rapid and highly localized Ca^{2+} spikes may co-occur or evolve into slower global $[Ca^{2+}]_i$ changes that are either transient, repetitive or sustained. Neuronal $[Ca^{2+}]_i$ rises mainly rely on Ca^{2+} entry via voltage- and receptor-operated plasma membrane channels, evoking highly localized and precisely timed $[Ca^{2+}]_i$ increases that ensure a fast, focal and timed neurotransmitter release from synaptic terminals [12]. In contrast, macroglial (astrocytes and oligodendrocytes) as well as microglial Ca^{2+} signaling mechanisms mostly rely on Ca^{2+} release from the ER. This creates a longer-lasting $[Ca^{2+}]_i$ elevation that is hypothesized to control a slower, and perhaps more sustained release of gliotransmitters [15]. The activation of store-operated Ca^{2+} entry (SOCE) following the depletion of the ER Ca^{2+} store, is equally important for shaping glial Ca^{2+} signals [117]. It gives rise to a sustained Ca^{2+} signal which may significantly outlast the periods of ER Ca^{2+} release induced by metabotropic receptor stimulation [17]. The key molecular players of SOCE are the stromal interaction molecules, which sense the luminal ER Ca^{2+} levels and control the opening of plasma membrane Orai channels [118,119]. In addition, Transient Receptor Potential (TRP) channels of the canonical family (TRPC) may contribute to SOCE [120], but this remains controversial [121].

The ER is the largest and most controlled intracellular Ca^{2+} store [122]. Generally, Ca^{2+} release from the ER is mediated by two families of receptor channels, IP_3 receptors (IP_3Rs) and ryanodine receptors (RyRs), which are both represented by three isoforms (IP_3R1–3 and RyR1–3) [123–126]. Ca^{2+} itself is an activator of RyR channels and a potent regulator of IP_3-induced Ca^{2+} release; Ca^{2+} thus provides a regenerative autocatalytic mechanism which is referred to as Ca^{2+}-induced Ca^{2+} release [127]. The primary activation mechanism of IP_3Rs is IP_3 binding. IP_3 is generated by phospolipase C (PLC), which is linked to a multitude of plasmalemmal metabotropic receptors. There are 13 different PLC isoforms, which are divided into six different classes (PLCβ, PLCγ, PLCδ, PLCε, PLCζ and PLCη) based on their structure. These PLC proteins can be activated via different mechanisms including the stimulation of G-protein-coupled receptors (GPCRs), receptor and non-receptor tyrosine kinases, the activation of the small G-protein Ras, or by an increase in $[Ca^{2+}]_i$ [128]. PLC catalyzes the cleavage of phosphoinositol-4,5-bisphosphate into diacylglycerol and IP_3. The latter diffuses inside the cell and binds its receptors located on the ER surface, resulting in IP_3-induced Ca^{2+} release (IICR) from the ER [116]. Astrocytes are equipped with a large repertoire of neurotransmitter receptors, many of which couple to the activation of PLC, production of IP_3 and subsequent release of Ca^{2+} from internal stores [37,129]. At low levels of stimulation, single IP_3R channels open resulting in brief and localized Ca^{2+} blips, but usually, coordinated opening of clusters of IP_3Rs takes place, giving rise to Ca^{2+} puffs. Under certain conditions, these localized events may expand and recruit nearby ER Ca^{2+} channels to generate an *intra*cellular Ca^{2+} wave sweeping over the cytoplasm thereby globalizing the Ca^{2+} response within the cell [130]. The spatiotemporal organization of Ca^{2+} signals thus tightly depends on the rearrangement of the Ca^{2+} channels on the ER surface, as well as their close contact with other Ca^{2+}-sequestering organelles such as mitochondria.

It becomes increasingly recognized that mitochondria play an important role in shaping the Ca^{2+} signals [115,131]. Consequent to proton extrusion by the electron transfer chain, required for ATP synthesis, mitochondria have an internally negative electrical potential

Table 2
Mechanisms of Ca^{2+} transport between cytoplasm and extracellular environment or intracellular stores.

Passive downhill	Transport mode	Remarks
EC to cytoplasm	–Voltage-operated channel –Receptor-operated channel –Store-operated channel –Second messenger-operated channel –Non-selective channel	
ER to cytoplasm	–IP_3R –RyR –ER leak channels[a]	
between cytoplasm and mitochondria	–MCU –VDAC –PTP	MCU is a highly selective Ca^{2+} channel across the IMM while VDAC is the major regulator across the OMM PTP opening is associated with pathological conditions and results in Ca^{2+} transport from mitochondria to the cytoplasm
Golgi to cytoplasm	IP_3R	
lysosomes and endosomes to cytoplasm	TPC	
Active uphill	**Transport mode**	**Remarks**
cytoplasm to EC	PMCA	
cytoplasm to ER	SERCA	
cytoplasm to Golgi	–SPCA –SERCA	
Secondary active uphill	**Transport mode**	**Remarks**
plasma membrane	NCX	The energy of the Na^+ or H^+ gradient is used to extrude Ca^{2+} from the cell or from the mitochondria, however, it can work in reverse mode depending on the transmembrane Na^+, H^+ or Ca^{2+} gradients and membrane depolarization
mitochondrial membrane	–NCX –H^+/Ca^{2+} antiporter	

This list summarizes the most important Ca^{2+}-permeable channels and pumps responsible for the Ca^{2+} transport between the compartments. Additional less-known mechanisms are reported to contribute but are not mentioned in the scheme.
(EC, extracellular environment; IMM, inner mitochondrial membrane; MCU, mitochondrial Ca^{2+} uniporter; NCX, Na^+/Ca^{2+} exchanger; OMM, outer mitochondrial membrane; PMCA, plasma membrane Ca^{2+} ATPase; PTP, permeability transition pore; SERCA, sarco-endoplasmic reticulum Ca^{2+} ATPase; SPCA, secretory pathway Ca^{2+} ATPase; TPC, two-pore channels; VDAC, voltage-dependent anion channel).
[a] ER leak channels remain unidentified up to date, but IP_3R, RyR, TRP and Panx channels have been suggested to contribute to the Ca^{2+} leak.

that attracts Ca^{2+} to enter the mitochondrial matrix. Mitochondrial Ca^{2+} uptake is mediated by the voltage-dependent anion channel (VDAC) located at the outer mitochondrial membrane and the mitochondrial Ca^{2+} uniporter (MCU) which is situated in the inner mitochondrial membrane [132–136]. Mitochondria accumulate Ca^{2+} more effectively when they are close to sites of high Ca^{2+} concentration [137,138]. They are physically and functionally connected to the ER, separated by a distance in the range of 10–30 nm [139,140] that facilitates the uptake of Ca^{2+} released by the ER [141]. Contact sites between the two organelles are known as mitochondria-associated ER membranes or MAMs [142,143]. These are intracellular lipid raft-like structures intimately involved in cholesterol and phospholipid metabolism, and in Ca^{2+} homeostasis by providing direct transfer of ER-derived Ca^{2+} to the mitochondria [144–149]. Approximately 75 proteins have been reported to be associated with the MAMs [150]. Mitofusin 2 proteins are important for the tethering of the two organelles [151,152] and other proteins such as phosphofurin acidic cluster sorting protein 2, are reported to stabilize and regulate the interaction [153]. An interaction between the IP_3R1 and VDAC1 via the chaperone 'glucose regulated protein 75' favors Ca^{2+} transfer [151]. Upon IICR, local microdomains with Ca^{2+} concentrations exceeding ~10 μM ('hotspots') are created in the vicinity of mitochondria [137,141], favoring mitochondrial Ca^{2+} entry via the MCU that has an intrinsic low Ca^{2+} affinity (EC_{50} is 10–20 μM) [138,154]. A major role of mitochondrial Ca^{2+} entry and consequent increase of matrix $[Ca^{2+}]$ consists in the stimulation of ATP production by activating Ca^{2+}-sensitive dehydrogenases of the Krebs cycle, regulating the activity of the ATP synthase and promoting the supply of oxidizable substrates [131,155–157]. Once the cytosolic Ca^{2+} has returned to its resting level, mitochondrial Na^+/Ca^{2+} exchangers (NCX) or H^+/Ca^{2+} antiporters transport Ca^{2+} from the mitochondrial matrix into the cytoplasm, from where it is either recycled to the ER or removed from the cell [158,159]. MAMs thus emerge as signaling hubs controling oxidative cell energy metabolism and alterations at the MAMs are implicated in a wide spectrum of diseases, including ischemia and neurodegenerative disorders (see Section 5, and [148,160]).

Ca^{2+} waves are not always restricted to the cytosol of a single cell, but can cross the cell boundaries to form an ICW (Fig. 2). GJs offer the most direct route for ICW propagation by allowing the transfer of Ca^{2+} and IP_3. Ca^{2+} diffusion in the cytoplasm is slow (diffusion constant in the order of 13 to 65 $\mu m^2/s$) due to the presence of slowly mobile Ca^{2+} binding proteins [161,162]. In contrast, the diffusion of IP_3 (MW 420 Da) is faster (diffusion constant ~283 $\mu m^2/s$) and GJs are more permeable to IP_3 than to Ca^{2+} (100-fold difference) [161,163]. Thus, Ca^{2+} can pass through GJs, but it reaches the adjacent cell with some delay compared to IP_3. IP_3 therefore stands out as the primary Ca^{2+} signaling molecule passing via GJs [164]. Notably, GJs display selective permeability toward IP_3 depending on their Cx composition. Niessen and colleagues demonstrated that microinjection of IP_3 into HeLaCx32 cells triggered ICWs that were 3- to 4-fold more widespread than in HeLaCx26 cells and 2.5-fold larger than in HeLaCx43 cells [165]. Cyclic adenosine diphosphoribose (cADPR; MW 541 Da) is another GJ-permeable intercellular signaling molecule that triggers ICWs upon injection in astrocytes, but Ca^{2+} wave propagation is slower as compared to IP_3-based ICWs [166]. cADPR is synthesized from NAD^+ by the ADP-ribosyl cyclase CD38, which is located on the cell surface and intracellular membranes. cADPR functions as a Ca^{2+} messenger by modulating the Ca^{2+} sensitivity of RyRs and appears to play an important role in Ca^{2+} signaling in the CNS, including in glial cells [167,168]. Apart from GJIC, non-junctional paracrine signaling also contributes to the propagation of ICWs (Fig. 2) [9–11]. The extracellular messengers involved are in most cases ATP or glutamate [169–173], but others such as NO [174] and NAD^+ [175] have also been suggested. Release of ATP and glutamate has been documented to occur via exocytosis or diffusion through Cx HCs, Panx channels, or $P2X_7$ receptor channels [72,73,94,171,176–180]. The downstream effect of these messengers involves the GPCR-PLC-IP_3 signaling axis or Ca^{2+} entry via plasma membrane

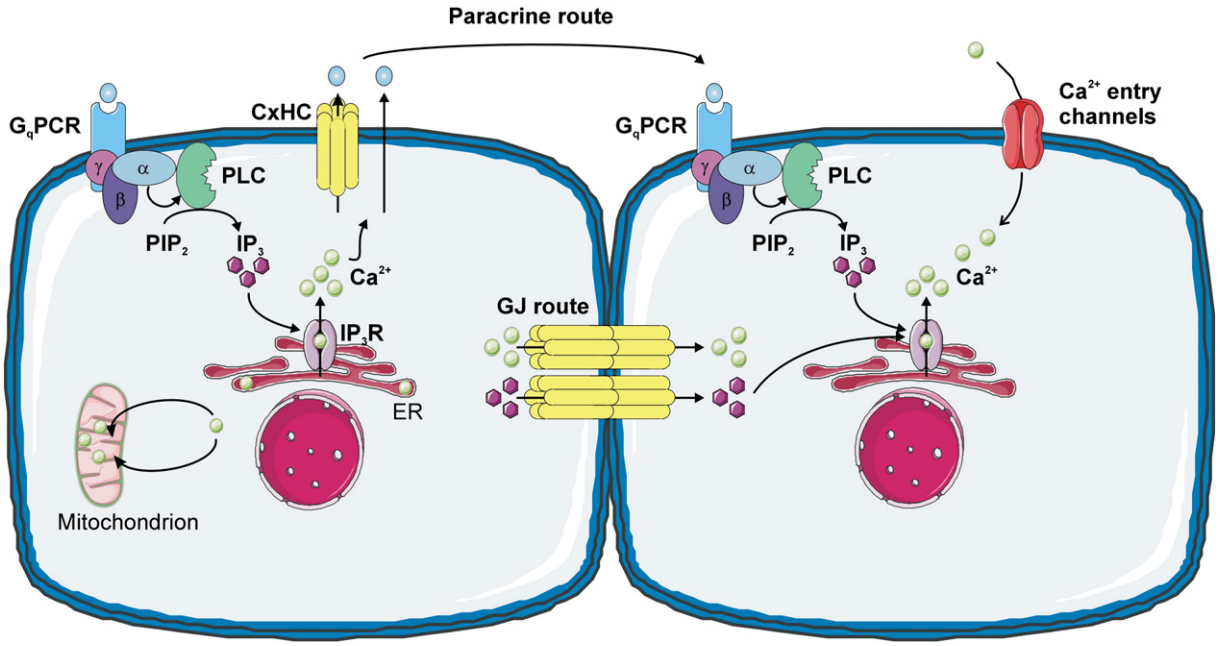

Fig. 2. Mechanisms underlying intercellular Ca^{2+} signaling. The activation of plasma membrane GPCRs results in the PLC-mediated synthesis of IP_3 and subsequent IICR from the ER. Mitochondrial Ca^{2+} uptake prevents Ca^{2+} from reaching deleterious levels in the cytoplasm. The intracellular Ca^{2+} signal can propagate to neighboring cells via two routes, a direct one involving GJs, with IP_3 as the primary coordinating messenger, and an indirect one that is mediated by the release of paracrine messengers. Here, ATP and glutamate are the prototypical paracrine molecules released into the extracellular environment via multiple mechanisms including HCs, a vesicular pathway or channels such as the $P2X_7$ receptor. They diffuse in the extracellular space and activate their corresponding GPCRs or channels on neighboring cells. Regenerative mechanisms include the Ca^{2+}-dependent activation of PLCδ or stimulation of paracrine release mechanisms. (CxHC, connexin hemichannel; ER, endoplasmic reticulum; GJ, gap junction; G_qPCR, G-protein coupled receptor; IICR, inositol 1,4,5-trisphosphate-induced Ca^{2+} release; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; IP_3, inositol 1,4,5-trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor).

channels. Cx43 HCs may also contribute to the release of NAD^+ that is converted extracellularly into cADPR. The plasma membrane CD38 enzyme subsequently transports cADPR back into the cell [76]. In most cases, ICW propagation is sustained by both the GJ and paracrine pathway, supported by regenerative steps which result in more extensive ICWs [9]. GJ-mediated regenerative processes rely on Ca^{2+}-triggered regeneration of IP_3 via the activation of PLCδ [163]. Paracrine messenger regeneration is supported by the Ca^{2+}-dependence of vesicular but also HC release mechanisms [86,181–183].

4.2. Intercellular Ca^{2+} signaling in the NGVU

Although several tissues and organs display ICWs or in more general terms 'intercellular Ca^{2+} signaling' (as the typical concentric wave aspect is not always present), the case is especially strong for the brain, where Ca^{2+} is a basic signal for glial network communication (Fig. 3). Evidence demonstrating Ca^{2+} signals propagating over tens to hundreds of astrocytes in cell culture started to appear more than 20 years ago [169–171,179,184–187]. Although the true function of inter-astrocyte Ca^{2+} signals is still unclear, the central position of astrocytes in the NGVU, making contacts with neurons, vascular cells and microglia (Fig. 3) has been a major factor in driving a continued interest and experimental exploration. There is now evidence for glial ICWs in more complex ex vivo preparations such as hippocampal and cortical slices [50,174,188–191]. For example, Weissman and colleagues demonstrated ICWs in radial glia that postnatally transform into astrocytes in the proliferative cortical ventricular zone of the developing neocortex [188]. The latter require Cx HCs, $P2Y_1$ receptors and IICR, and are proposed to regulate cortical neuron proliferation. More recently, advances made in the field of two-photon microscopy have enabled visualization of astrocyte Ca^{2+} dynamics (not necessarily waves) in vivo (Table 3 and [16,17,21,192–194]), either arising spontaneously [16,17] or in response to somatosensory [195] or visual stimulation [194]. Spontaneously occurring wave-like Ca^{2+} signal propagation has been observed in glial cells of the hippocampus [18], the neocortex [17], the cerebellum [16,19] and the retina [196] (Table 3). Local application of bicuculline to increase neuronal activity by suppressing GABA-signaling triggers astrocytic ICW activity in vivo [193] but evidence supporting astrocytic ICW generation in response to physiological levels of stimulation is still lacking.

Astrocytic ICWs have been reported to spread at a uniform speed of 5–20 μm/s, which is several orders of magnitude slower than the propagation of neuronal electrical signals [16,188]. In vivo, ICWs propagate over astrocyte networks with even lower velocities in the order of 8–10 μm/s [197]. The relative contribution of paracrine/purinergic signaling and GJIC to ICWs is likely to depend on brain region-specific factors [198] and on the nature of the applied trigger [188]. In acutely isolated retina, mechanical stimulation evokes ICWs among astrocytes which depend on GJIC, while the propagation from astrocytes to Müller cells involves purinergic, paracrine signaling [199]. In the corpus callosum and hippocampus, glial ICWs were blocked by purinergic receptor antagonists, but were insensitive to GJ blockers and the deletion of Cx43 or Cx30 expression using conditional Cx43(fl/fl):GFAP-cre mice and Cx30 −/− KO mice [198,200]. In contrast, in the neocortex, glial ICWs depend on functional GJs as well as ATP release [198]. There is cross-talk between the gap junctional and the paracrine pathways of ICW propagation: deletion of Cx43 in spinal cord astrocytes leads to an increase in paracrine, purinergic Ca^{2+} signaling by a switch in the P2Y receptor subtype, resulting in increased responses to ATP or uridine 5′-triphosphate [102]. Additionally, the cytoplasmic C-terminal domain of Cx43 modulates the activity of the $P2Y_1$ receptor in astrocytes via a protein–protein interaction between Cx43 and the $P2Y_1$ receptor, involving the Cx43 C-terminal SH3-binding domain [101].

Astrocytic $[Ca^{2+}]_i$ changes modulate synaptic transmission in in vitro astrocyte–neuron co-culture systems, the intact retina and hippocampal slices [61,201–203]. Astrocytes remove and recycle K^+ ions and neurotransmitters from the synaptic cleft [204], but also respond to neurotransmitters by means of a large family of membrane receptors [37,192,205]. The ensuing signaling, often involving $[Ca^{2+}]_i$ changes, triggers the release of gliotransmitters such as glutamate, D-serine,

ATP, adenosine and GABA [31–34,178,206–209]. These influence presynaptic neurotransmitter release, excitatory postsynaptic firing and extrasynaptic neuronal activity [207,210,211], neuronal circuit plasticity [212], and neuronal survival (see Section 5). The source of cytosolic Ca^{2+} that mediates gliotransmitter release is dual; it is predominately derived from the ER involving both IP_3Rs and RyRs [213], but also involves Ca^{2+} influx from the extracellular environment, likely mediated by TRPC1 channels [214]. Additionally, mitochondria modulate exocytotic glutamate release from astrocytes, since inhibiting mitochondrial Ca^{2+} accumulation increases $[Ca^{2+}]_i$ and enhances glutamate release

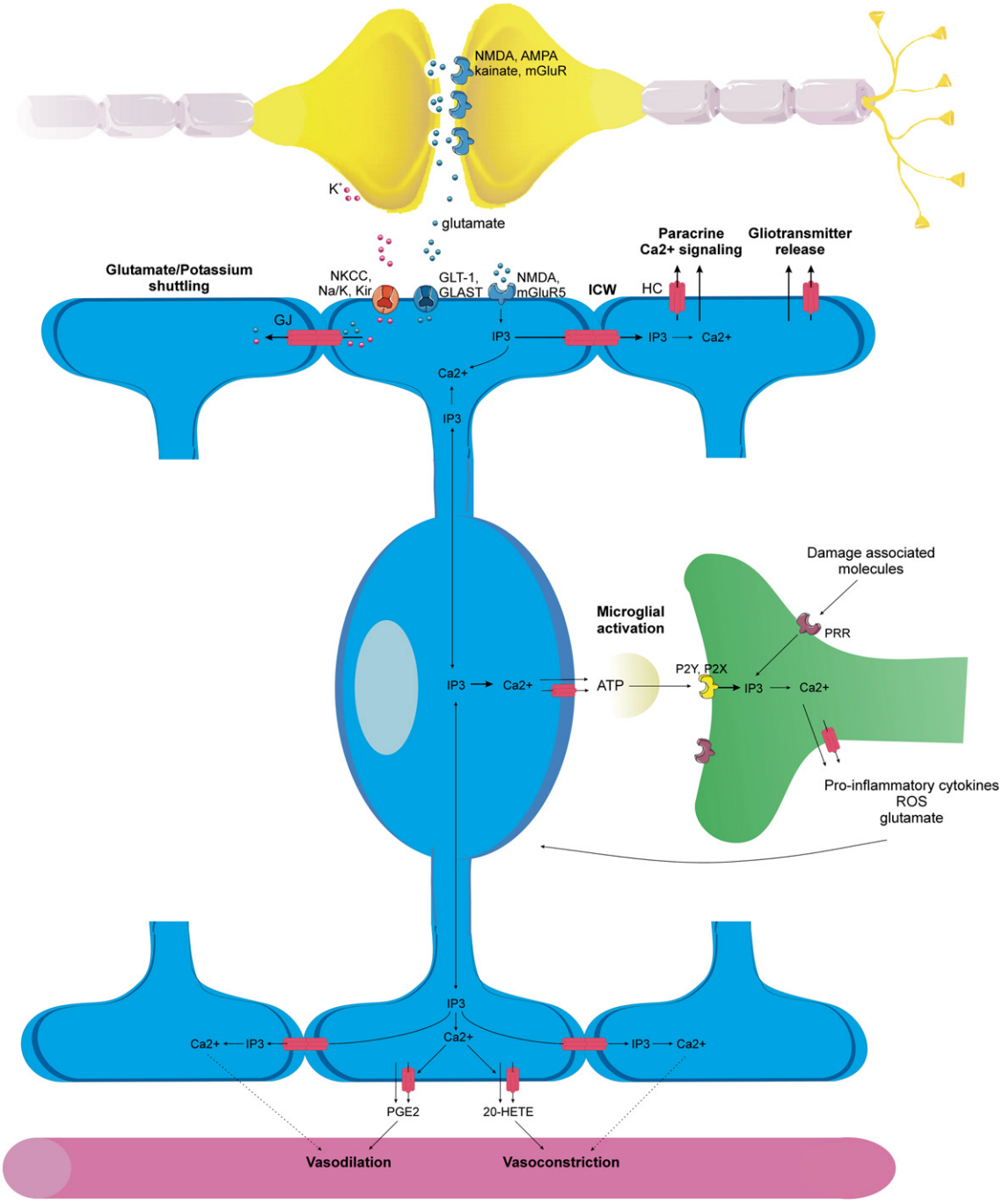

Fig. 3. Ca^{2+} signaling at the NGVU. At the level of the synapse, astrocytes perform three key functions. By removing and recycling byproducts of action potential firing, including glutamate and K^+ ions, from the synaptic cleft, astrocytes protect neurons from excitotoxicity. Additionally, astrocytes are activated by neurotransmitters like glutamate to which they respond with an increase in $[Ca^{2+}]_i$. Subsequently, astrocytes release so-called gliotransmitters via which they influence synaptic activity and neuronal circuit plasticity. The increase in $[Ca^{2+}]_i$ can be propagated to neighboring astrocytes via either the gap junctional or the paracrine route which will allow astrocytes to modulate remotely located synapses. The Ca^{2+} signal raised by synaptic activity will additionally propagate within the astrocytes toward the astrocytic endfeet that surround the blood vessels. Here, Ca^{2+} will stimulate the release of vasodilators and/or -constrictors. As such, astrocytes are important players in neuron-to-vessel signaling. Again, the propagation of Ca^{2+} signals between well-coupled endfeet will allow a coordinated response along the vessel wall. Finally, in pathological conditions, astrocytic Ca^{2+} signals may be involved in the activation of microglia. ATP release, possibly via HCs, is of significant importance in this process. Microglia may also be activated by damage-associated molecules, all of which lead to a microglial Ca^{2+} increase. This rise in $[Ca^{2+}]_i$ may ultimately lead to the release of pro-inflammatory molecules that will signal back to astrocytes, contributing to astrogliosis. (20-HETE, 20-hydroxyeicosatetraenoic acid; GJ, gap junction; GLAST, glutamate/aspartate transporter; GLT-1, glutamate transporter 1; HC, hemichannel; IP_3, inositol 1,4,5-trisphosphate; mGluR, metabotropic glutamate receptor; Kir, inwardly rectifying K^+ channel; NKCC, $Na^+/K^+/Cl^-$ cotransporter; Na/K, Na^+/K^+-ATPase; PGE_2, prostaglandin E_2; PRR, pattern recognition receptor; ROS, reactive oxygen species).

[215]. Notably, the Ca^{2+}-dependent glutamate release from astrocytes and its subsequent modulation of synaptic activity is challenged by a study performed on IP_3R2 KO mice [216]. Several lines of evidence suggest that this subtype is the primary IP_3R expressed by astrocytes [217,218]. Ablating IP_3R2 eliminates both spontaneous and GPCR-mediated increases in astrocytic Ca^{2+}, while neuronal GPCR-dependent Ca^{2+} increases remain intact. However, silencing astrocyte Ca^{2+} signaling provoked by IP_3R2 KO did not significantly affect perisynaptic glutamate levels nor did it alter excitatory CA1 pyramidal neuronal synaptic activity [216].

At the vascular side, astrocytic Ca^{2+} signaling links to blood flow regulation, metabolic trafficking, BBB function and water homeostasis [50]. In situ, astrocytes express $P2Y_2$ and $P2Y_4$ receptors and Cx proteins, both involved in Ca^{2+} signaling, as well as aquaporin 4 (AQP4) involved in water homeostasis at their perivascular endings [50]. This extraordinary high expression of basic Ca^{2+} signaling elements supports wave-like propagation of Ca^{2+} signals between rows of endfeet to influence vascular SMCs and blood vessel diameter, as observed in brain slices [219]. At present, it is not known whether endfeet Ca^{2+} signaling also influences capillary endothelial cells and BBB function. Cell culture studies have suggested propagation of ICWs between astrocytes and endothelial cells [68,220] but this could not be confirmed in cortical slice studies [50]. Possibly, this is related to the presence of the basal lamina interposed between endothelial cells and astrocytes, and the fact that ATP is a short-distance messenger that is rapidly degraded by ectonucleotidases [221].

The evidence that neuronal activity-triggered astrocytic Ca^{2+} signaling modulates arteriolar blood flow is particularly strong and supported by brain slice as well as in vivo animal studies [194,222–224], although at least one recent study challenges this view [225]. Electrical stimulation of neuronal afferents results in the activation of astrocytic metabotropic glutamate receptors (GluRs), giving rise to a $[Ca^{2+}]_i$ increase and release of PGE_2 that induces a vasodilation of adjacent cortical arterioles [223,224,226]. Follow-up work indicated that the $[Ca^{2+}]_i$ increase in astrocytes is pursued by $[Ca^{2+}]_i$ changes in vascular SMCs: vasodilation was accompanied by a suppression of Ca^{2+} oscillations in SMCs, likely mediated by astrocyte-derived carbon monoxide. The SMC response is furthermore abolished in isolated arterioles where astrocytes are absent and in brain slices where astrocytes are ablated by the gliotoxin L-alpha-aminoadipic acid (L-AAA), that is reported to target astrocytes by a yet unknown mechanism [38,227–229]. Astrocytic $[Ca^{2+}]_i$ changes have, in addition to triggering vasodilation, also been reported to provoke vasoconstriction mediated by the arachidonic acid metabolite 20-hydroxyeicosatetraenoic acid [219]. One explanation for these opposite vascular reactions relates to perivascular K^+ levels. The threshold concentration of perivascular K^+ for inducing a vasodilatory response is 20 mM. When $[K^+]$ exceeds this threshold, the vascular respons converts into a constrictive one. Large conductance Ca^{2+}-sensitive K^+ channels, that are strongly expressed in astrocytic endfeet [230], are decisive in determining these perivascular K^+ levels [231,232]. Another explanation is related to oxygen availability. The vasodilatory response to astrocytic $[Ca^{2+}]_i$ elevation is favored by low oxygen availability, which results in increased astrocytic glycolysis and consequent lactate release. This stimulates the extracellular accumulation of vasodilatory PGE_2 and adenosine [233]. Astrocytic lactate release may also result from the uptake of synaptically derived glutamate, thereby boosting glycolysis and contributing as a Ca^{2+}-independent astrocytic influence [226]. A differential vascular effect of astrocytic $[Ca^{2+}]_i$ elevation may be responsible for an increased blood flow in areas experiencing neuronal activation while reducing the flow to inactive regions vascularized by vessels branching from the same artery. Importantly, the extent of vasomotor responses seems to depend on the number of endfeet that are activated [222]. Spatially confined $[Ca^{2+}]_i$ changes confer a dimensionally restricted control over the arteriolar diameter [194,219,224,234]. By contrast, a sufficiently large increase in $[Ca^{2+}]_i$ is capable of inducing an ICW that propagates along foot processes enwrapping the vascular wall, thereby mediating a more expanded vascular response [50,219] which might be involved in the vasodilation of upstream pial arteries [235]. The role of glial Cx channels in this process remains to be fully established but at least one report highlights the necessity of Cx43 in vasodilatory responses [59]. It is unknown whether this concerns endothelial or astrocytic Cx43 but vascular Cx37 and Cx40 at least did not appear to be involved.

Alterations in local blood flow in response to neuronal activity are known as functional hyperemia or neurovascular coupling, and secure an adequate supply of glucose and oxygen under conditions of increased demand. Neurovascular coupling is adjoined by coupling of neuronal activity to changes in energy metabolism that is compartmentalized in astrocytes and neurons. According to the classical view, glucose is the main fuel for both neurons and astrocytes. However, this view has been challenged by the astrocyte–neuron lactate hypothesis which states that the uptake of glucose predominantly takes place in astrocytes. Subsequently, lactate is produced by astrocytes in an activity-dependent, glutamate-mediated manner, and is transferred to active neurons, where it's been converted into pyruvate that fuels the Krebs cycle [236–239]. Additionally, coupling to transport over BBB endothelial cells, dubbed neurobarrier coupling, has also been proposed [238,240]. Each of these processes may be regulated by changes in $[Ca^{2+}]_i$ as well [241–245].

5. Aberrant Ca^{2+} signaling in neurogliopathologies

Spontaneous ICWs have been observed in vitro in cultured astrocytes starting from the 90s [184]. However, it is speculated that such spontaneous ICWs are probably an artifact of cultured cells [246]. In particular, the intensity/duration of the stimuli required to evoke these ICWs in vitro is often in a supraphysiological range [9]. Although frequently observed in cultured cells, several authors did not observe ICWs under basal/physiological levels of neuronal activity in vivo [21,22,25,194,195]. In contrast, a handful of publications have reported the occurrence of ICWs in vivo in several disease states such as ischemia [20], epilepsy [25,26], AD [21,22], brain trauma [23,24] and cortical spreading depression [247] (Table 3), suggesting that pathological conditions are more favorable toward the triggering and/or the propagation of ICWs. However, many important questions still remain: how are these glial ICWs initiated, how are they propagated (paracrine versus GJIC) and how do glial ICWs contribute to the pathogenesis and disease progression?

5.1. Pathological triggers as potent inducers of intercellular Ca^{2+} waves

A decrease in $[Ca^{2+}]_e$, known to evoke ICWs [187,248], has been reported to occur in hypoglycemia, ischemia, epilepsy, and CNS trauma [249–252]. In addition, mild declines in brain interstitial Ca^{2+} levels may take place in response to neuronal stimulation [253,254]. Various trigger mechanisms for the low $[Ca^{2+}]_e$-induced ICWs have been proposed with the most plausible one pointing to CxHC mediated ATP release that acts as a point source from trigger cells [169]. Mechanical stimulation and trauma induce ICWs that can propagate hundreds of μm in in vitro model systems, depending on the magnitude of the stimulus [23,24,255,256]. Wave-like Ca^{2+} dynamics in vivo generally appear to involve tens of astrocytes [16,26,257]. Amyloid-β (Aβ)-peptide, the major component of senile plaques in Alzheimer patients, increases the amplitude, velocity and distance of ATP- and GJ-mediated ICWs in astrocyte cultures [258]. Moreover, pathologically relevant concentrations of Aβ (nM to μM range) were able to induce astrocytic ICWs with a delay of minutes, suggesting a reorganization in terms of chemical Ca^{2+} excitability threshold and/or communication properties of the intercellular network [259]. Of note, picomolar amounts of Aβ that are not associated with pathology, do facilitate spontaneous Ca^{2+} transients in astrocytes but do not affect ICW parameters [260], pointing to an increase in Ca^{2+} excitability. In amyloid precursor protein (APP)/presinilin 1 (PS1) double transgenic mice that express mutant human PS1-ΔE9 and chimeric mouse/human APPswe, Aβ plaques nearly double

Table 3
Overview of triggers and mechanisms involved in in vivo intercellular Ca^{2+} signaling.

Trigger	Cell types[a]	Propagation mechanism	Remarks	Reference
Spontaneous				
	Astrocytes/neurons	ND	ICWs observed in astrocytic network	[17]
	Hippocampal astrocytes	Purinergic signaling/Cx channels	High-speed ICW-like propagations ('glissandi') involving hundreds of astrocytes Glissandi depend on neuronal activity Associated with a reduction in blood flow	[18]
	Retinal glia	Purinergic signaling	ICWs propagated through Müller cells, not through astrocytes Aging increases spontaneous ICWs due to more ATP release Associated with a reduction in blood flow	[196]
	Bergmann glia	ND	Aging increases spontaneous ICWs Accompanied by $[Ca^{2+}]_i$ increases in Purkinje neurons, but no change in neuronal activity Reduces brain oxygen tension	[19]
	Bergmann glia	Purinergic signaling	Recurring waves extend from the same foci	[16]
Neuronal activity				
Bicuculline ($GABA_A$ receptor blocker)	Astrocytes			[193]
Whisker stimulation	Astrocytes	Glutamatergic signaling	No ICWs reported	[195]
Visual stimuli	Astrocytes	Glutamatergic signaling	No ICWs reported	[194]
Glutamate uncaging/visual stimuli	Microglia	Neuronal Panx1 HCs/ purinergic signaling	No ICWs reported Microglia migrate to and make contact with activated neurons Microglial–neuronal contact downregulates neuronal activity	[384]
Ischemia				
Photothrombosis	Astrocytes	Glutamatergic	The Ca^{2+} chelater BAPTA-AM reduced the infarct volume	[20]
Alzheimer's disease				
APP/PS1 mice	Astrocytes	ND	Astrocytic $[Ca^{2+}]_i$ elevated, independently from distance to Aβ plaques ICWs induced near plaques and spread radially	[21]
3xTgAD mice PDAPP mice	Astrocytes	ND	In contrast to AD mice, no spontaneaous ICWs or ICWs in response to photo-activation of IP_3 were observed in control mice	[22]
Traumatic injury				
Brain cortical impact	Astrocytes	Purinergic signaling	Influences neuronal network activity and evokes neuronal death as evidenced from experiments conducted on neuron–glia co-cultures and organotypic slice cultures	[24]
Laser ablation	ND	Glutamatergic signaling	ICWs not dependent on ATP or Cx channels ICW-evoked ATP release attracts microglia Local photo-activation of caged IP_3 mimicks the microglial injury response	[23]
Laser ablation/mechanical injury	Astrocytes	Purinergic signaling/Cx channels	Polarized Ca^{2+} gradient in astrocytes that guides microglia to the injury site No ICWs observed	[376]
Epilepsy				
Pilocarpine-induced status epilepticus	Astrocytes	Glutamatergic signaling	Evoke neuronal cell death Astrocytic Ca^{2+} signals are dependent on metabotropic mGluR5, while neuronal cell death relies on NMDAR activity	[25]
4-Aminopyridine-induced seizures	Astrocytes	ND	Evokes PDSs through glutamate release	[26]
Cortical spreading depression				
High $[K^+]_e$	Neurons/astrocytes		ICWs are observed in neurons and in astrocytes Astrocyte ICWs evoke vasoconstriction of intracortical vessels	[247]

[a] In which the Ca^{2+} responses were studied. (Aβ, amyloid-β; APP, amyloid precursor protein; BAPTA-AM, 1,2-bis(2-aminophenxy)ethane-N,N,N',N'-tetraacetic acid acetoxymethyl ester; Cx, connexin; HC, hemichannel; ICW, intercellular Ca^{2+} wave; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; PDS, paroxysomal depolarization shift; PS, presinilins)

astrocyte resting $[Ca^{2+}]_i$ and promote spontaneous Ca^{2+} activity that is communicated radially over at least 200 μm along the astrocytic network [21]. The ICWs do not rely on the presence of hyperactive neurons near the plaques [21,261], indicating that the increased astrocytic Ca^{2+} excitability is induced by Aβ exposure itself and is not the result of an enhanced electrical excitability of neurons. The augmentation in astrocyte $[Ca^{2+}]_i$ in response to Aβ can be mediated by Ca^{2+} store release (IP_3- and RyR-dependent) and SOCE [262]. Additionally, Aβ has been shown to bind the Ca^{2+}-sensing receptor, a GPCR that senses extracellular Ca^{2+} levels [263], or to enhance spontaneous Ca^{2+} signaling via nicotinic acetylcholine receptors in astrocytes [260]. Alternatively, intracellular accumulation of Ca^{2+} may be mediated by the pore-forming capacity of Aβ protein or possibly by creating a non-selective Ca^{2+} entry route by inducing oxidative stress and lipid peroxidation of the plasma membrane [264,265].

Another potential trigger for ICWs may originate from areas of cell death. Most, if not all, brain diseases are associated with cell death that is accompanied by the release of ATP and glutamate from the intracellular metabolic pool [266]. These neural/glial transmitters activate ionotropic and metabotropic receptors, with subsequent Ca^{2+} entry and IP_3-triggered ER Ca^{2+} release that may trigger ICWs [169–173,184,186]. Work from our research group on cultured glioma cells, has brought forward that both Cx43 GJs and HCs are involved in communicating cell death messages from cells undergoing apoptosis to healthy neighboring cells, a process known as 'bystander cell death' [267]. Importantly, we demonstrated that the passage of the Ca^{2+} messenger IP_3 through GJs is crucial for intercellular cell death communication. This work provided evidence that the physiological messenger IP_3 becomes a pathological intercellular messenger when the cells generating IP_3 are exposed to proapoptotic conditions [268,269]. Recent work from others supports this concept and demonstrates that HIV infection of astrocytes results in bystander apoptosis of uninfected astrocytes via the IP_3/Ca^{2+} signaling axis [270]. Thus, IICR is required for normal function and cell survival, but it can also be actively involved in apoptosis

induction, progression and propagation [269,271]. In fact, ER-mitochondrial Ca^{2+} transfer at the level of the MAMs plays a major role in cell death by providing proapoptotic Ca^{2+} transfer via IP_3R interaction with VDAC1 [143,272–276]. Additionally, numerous factors involved in apoptosis have been located at the ER–mitochondrial interface and modulate cell survival by directly or indirectly regulating IICR [277,278]. Recent evidence revealed that alterations in ER–mitochondrial Ca^{2+} communication, possibly by regulating IICR, may represent a common hit in several brain pathologies including ischemia [279,280] and neurodegenerative diseases such as AD and Parkinson's disease [150,281–286]. Although neurons themselves are the primary target of investigation in these studies, an increasing number of publications have demonstrated alterations in ER Ca^{2+} signaling in astrocytes, primarily in ischemic conditions and AD [280,287–290]. While the contribution of GJs to bystander cell death is straight forward, i.e. they facilitate the direct exchange of cell death and cell survival signals between cells, the role and functional consequences of HC opening on cell death is still poorly defined. Several possibilities have been put forward: (i) HC opening may help in setting off cell death by the excessive entry of Ca^{2+} or other toxic molecules and (ii) being a pore permitting diffusion in both directions, HCs could also contribute via the release of survival molecules or, more indirectly, via the release of paracrine messengers which induce a $[Ca^{2+}]_i$ rise in more distant cells [291,292].

Disturbances in astrocyte Ca^{2+} signaling combined with Cx-mediated Ca^{2+} signal communication may thus act to expand cell death and neurodegeneration. As discussed in the next sections, ICWs may possibly be involved in expanding the processes of reactive astrogliosis and microglial activation as well. The balance between astrogliosis, microglial activation and neurodegeneration may ultimately determine the level of destruction, neuroprotection and regeneration resulting from the pathological process.

5.2. A role for Ca^{2+} and connexins in astrogliosis?

Reactive astrogliosis, a defensive astrocytic response, is a common feature of many CNS disorders, including stroke, trauma, epilepsy, neurodegeneration, infection and autoimmunity [293]. However, despite its widespread observation, the role of as well as the cellular changes accompanying astrogliosis are poorly understood. Reactive astrogliosis is generally regarded as a defensive reaction towards injury which aims at isolating the damaged area from the rest of the brain tissue to facilitate restoration of the tissue surrounding the lesion. It generally appears as a hypertrophy and/or proliferation of astrocytes surrounding the lesion. Based on the severity of the changes, reactive astrocytes can be subdivided in two different classes, anisomorphic and isomorphic [294]. Anisomorphic astrocytes are characterized by robust hypertrophy and proliferation and evolve towards the formation of glial scar tissue that is composed of astrocytes and extracellular matrix [295]. Glial scar tissue surrounds the injured/lesioned tissue site and may therefore prevent its extension but it also plays a key role in regeneration failure because it inhibits axonal sprouting. In isomorphic astrocytes, the reactive changes are milder and often reversible, allowing regeneration of the tissue.

The upregulation of intermediate filament proteins, including glial fibrillary acidic protein (GFAP) and to a lesser extent nestin and vimentin, are often used as indicators for astrogliosis [296]. Other changes may appear in a context/disease-specific manner [297]. It is important to realize that many proteins associated with Ca^{2+} signaling are altered in reactive astrocytes. Genetic profiling of the astrocyte response towards pro-inflammatory mediators such as TGF-β and IFN-γ has recently uncovered the specific responses of different GPCRs towards inflammation and has revealed pronounced changes in the Ca^{2+} household during astrogliosis [298]. Likewise, an upregulation of the Ca^{2+}-entry channel TRPV4 coincides with the onset of astrogliosis during an hypoxic/ischemic insult [299], whereas the L-type Ca^{2+} channel $Ca_V1.2$ is upregulated in reactive astrocytes surrounding Aβ plaques [300]. Most interestingly, in several models, Ca^{2+} appears to be one of the early injury signals that initiates the signal transduction cascade for astrogliosis; e.g. through ER Ca^{2+} store release (via IP_3Rs and RyRs) and SOCE in Aβ-treated astrocytes [259,262] or following lipopolysaccharide (LPS) exposure [301], and through IICR [302] and Ca^{2+} influx in response to spinal cord and brain injury [303,304].

Cx43 is also reported to be one of the proteins modified in reactive astrocytes. Increased Cx43 expression has been detected in regions with astrogliosis induced by various CNS diseases including brain injury [305–308], spinal cord injury [309,310], brain ischemia [311,312], AD [313], epilepsy [314,315], and also following retinal ischemia [316,317]. Cx43 deletion in astrocytes causes a reduction of astrogliosis in brain ischemia and brain/spinal cord injury models [306,309,318–321]. Inversely, astrocytic Cx43 was decreased in the spinal cord of experimental autoimmune encephalomyelitis (EAE) mice (a model for multiple sclerosis [322]), and in response to a cortical lesion induced by kainic acid injection [323]. Thus, Cx43 may be up- or down-regulated, depending on the type of brain pathology, but probably also on the time scale, and the distance from the lesioned area. For example, excitotoxic induction of neuronal cell death in vivo lead to a strong decrease of Cx30 and Cx43 in reactive astrocytes located within the neuron-depleted zone, whereas increased Cx expression was found in reactive astrocytes at the periphery of the lesion [51]. Transient Panx2 expression was observed in reactive astrocytes in the hippocampus of adult rat brain subjected to ischemia/reperfusion injury [324].

There is limited evidence that ICWs could contribute to the generation of reactive astrocytes and glial scars e.g. after traumatic injury [255], ischemia [20], and Aβ exposure [259]. One paper has demonstrated an involvement of Cx-mediated ICWs to the expansion of astrogliosis [304]. Scratch injury applied to mouse cortical astrocyte cultures induced a $[Ca^{2+}]_i$ elevation along the scratch via Ca^{2+} entry, which was then disseminated to neighboring astrocytes as an ICW propagating via GJs. These increases in $[Ca^{2+}]_i$ switched on the JNK/c-Jun/AP-1 pathway to upregulate GFAP expression. Dampening the $[Ca^{2+}]_i$ changes with intracellulary-loaded BAPTA in an in vivo stab wound model, reduced the expression of GFAP and the extent and size of glial scars, supporting the involvement of Ca^{2+} signaling [304].

5.3. Neuronal cell death, a consequence of astrocyte network distortion?

Excitotoxicity, induced by excessive glutamate release and subsequent activation of Ca^{2+} and ROS signaling, is a major trigger for neuronal cell death [325,326]. Astrocytes coupled by GJs normally act to promote neuronal survival after a pathological insult by scavenging ROS (astrocytes contain high concentrations of antioxidant molecules such as glutathione and ascorbate) and by spatial buffering of extracellular K^+ and glutamate as set out in Section 3. However, as things get rough, glial homeostatic mechanisms can be altered which rapidly provides the astrocytic network with killer functions including the exacerbation of neuronal damage by decreased glutamate or K^+ uptake or by increased release of glutamate, ATP or inflammatory cytokines [319,327–331]. Most notably, ICWs spreading over the astrocytic network may promote astrocytic release of these messengers thereby worsening neuronal damage. The dual role of astrocytes implicates that a precise regulation of their response may determine the outcome of CNS pathology.

Astrocytic ATP release combined with extracellular glutamate accumulation promotes neuronal cell death [327] and at millimolar extracellular ATP concentrations it contributes to astrocytic cell death via the activation of $P2X_7$ receptors [332]. On the other hand, ATP is rapidly degraded to adenosine, which can affect neuronal functioning as it inhibits excitatory activity and presynaptic neurotransmitter release [254,333]. ATP may also contribute to myelin disturbances and axonal degeneration; ischemia-induced oligodendroglial death shows hallmarks of a Ca^{2+}-dependent excitotoxic pathway which involves the activation of N-methyl-D-aspartate receptors (NMDARs) and $P2X_7$

receptors that are activated by ATP released through Panx channels [334]. Panx1 channels were also suggested to function as large pores associated with the $P2X_7$ receptor [335,336], including in astrocytes [93]. Panx1 co-immunoprecipitates with $P2X_7R$ and inhibition of Panx1 prevents $P2X_7R$-mediated dye uptake [335,336]. In addition, functional NMDAR have been identified in astroglial cells (reviewed in [337]) and excess activation results in a Ca^{2+} influx that may spread through GJs composed of Cx43 and Cx47 to oligodendroglia, evoking apoptosis in the latter [338]. Finally, astrocytes produce and release a wide variety of inflammatory molecules including cytokines, chemokines and prostaglandins [339–341], which provides a mutual communication pathway between astrocytes and microglia (see Section 5.4). Astrocytes may be involved in anti-inflammatory processes including scar formation [342], or pro-inflammatory cytokine release may damage cells by e.g. increasing the Ca^{2+}-dependent release of glutamate [343]. Among the cytokines expressed by astrocytes, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) have received considerable attention because they activate CxHCs and exert pro-inflammatory effects in the CNS [331,344]. Inhibition of Panx1 prevents activaton of innate immunity and secretion of pro-inflammatory cytokines through the pattern recognition receptors NLRP1 and NLRP2 [345,346]. Panx1 channels, $P2X_7$ receptors and CxHCs may thus act in concert during the course of neuroinflammation.

5.4. Neuroinflammation, a combined effort between activated astrocytes and microglia

Ischemia, trauma and neurodegenerative diseases such as AD, amyotrophic lateral sclerosis (ALS), Huntington's disease and Parkinson's disease are some of the pathologies which are accompanied by inflammatory events [347,348]. Microglial cells form the innate immune defense system of the CNS. They continuously scan the brain parenchyma for damage signals by which they are activated. Once activated, microglial cells migrate to the site of injury, proliferate, and phagocytize cells and cellular compartments [349]. They accumulate around degenerating neurons and reactive astrocytes in various CNS disorders [347,348] and show diverse activated phenotypes depending on the pathology and the damage signal or chemoattractant that is released [350,351]. The best known chemoattractant sensed by microglia is ATP [352]. Several neuropeptides such as angiotensin II, bradykinin, endothelin, galanin and neurotensin are also chemoattractants for microglia [353]. Most of these molecules activate microglia by triggering a $[Ca^{2+}]_i$ elevation via plasma membrane Ca^{2+} channels such as ionotropic P2X receptors, IICR and the reverse mode of the NCX [351,354]. Microglia can also be activated by an Aβ-induced $[Ca^{2+}]_i$ surge, after which they secrete pro-inflammatory and neurotoxic factors [355,356].

Activated microglia release a large number of substances including ATP, glutamate, cytokines like TNF-α, superoxide radicals and neurotrophins that can either act detrimental or beneficial for the surrounding cells. They communicate with neurons and macroglial cells through paracrine factors [357]. Activated microglia express Cx32, Cx36 and Cx43 [357]. It is conceivable that the paracrine signaling molecules, some of which have a MW < 1.5 kDa, may be released via HCs. There is in vitro evidence for microglial glutamate release via HCs upon exposure to TNF-α [358]. Blocking HC-mediated glutamate release via different pharmacological substances (see Section 5.5) furthermore protects neurons from ischemic brain injury, attenuates EAE, and suppresses disease progression in ALS and AD mice in vivo [359–361]. Astrocytes can rescue neurons from microglial glutamate-induced death [362] but their glutamate-uptake capacity can also be hampered by microglial glutamate release via downregulation of the astrocytic GLAST glutamate transporter, thereby worsening extracellular accumulation of glutamate [363]. Cx32 HCs have been implicated in the release of glutamate from microglia [358]; however, at present, evidence for the expression and functional role of Cx32 remains poor. HCs composed of Cx43 are other candidates for mediating the release of paracrine messengers. This Cx is not expressed in quiescent microglial cells, but it is upregulated upon their activation, suggesting a role during inflammation. It has been recently shown that ATP release via microglial Cx43 HCs is involved in microglial death [364]. Finally, although GJs have been described in cultured microglial cells [365], GJIC between microglial cells as well as with other surrounding cells has recently been reported to be absent in vivo [366].

Conditioned media from activated microglia or direct application of a mixture of the pro-inflammatory cytokines TNF-α and IL1-β influence the Cx-based astrocytic communication network: GJIC is reduced while HCs are invariably reported to open [78,331,344,367–369]. Effectwise, the reduced GJ coupling will restrict the movement of glucose and lactate over the astrocytic network while the open HC pathway may provide non-specific glucose uptake from the interstitium [49,78]. The net balance of these diverse effects is currently not clear, but they might have serious implications for the metabolic status of astrocytes in brain inflammation. In terms of ICWs, pro-inflammatory cytokines can shift the ICW supportive pathway from GJIC to paracrine mechanisms [370]. Cytokines released by astrocytes can also influence microglial Ca^{2+} signaling [371] and were demonstrated to increase GJIC and induce HC opening in microglial cells [372,373].

$[Ca^{2+}]_i$ increases evoked by danger signals can propagate as ICWs, thereby possibly expanding inflammation. A recent study in zebrafish larval brain revealed that laser light-induced neuronal injury initiates an ICW that travels throughout the brain and attracts microglia to migrate to the injury site. Here, glutamate-dependent ICWs establish an ATP guidance cue that is responsible for transmitting positional information across the brain to $P2Y_{12}$-expressing microglia [23]. The propagation of the ICWs did not depend on Cx channels and ATP signaling, which contrasts with the observation that chemotactic microglial activation in mice is reduced by Cx channel blockers [374]. Although neurons, oligodendrocytes and endothelial cells are all candidates for releasing ATP upon injury, astrocytes are suggested to be the main cell type responsible for the rapid and long-range microglial response towards injury. Astrocytic ICWs trigger microglial responses in brain slices which appear to depend on the release of ATP [200,375]. Kim and Dustin [376] reported that laser-induced necrotic injury in vivo induces morphological changes in astrocytes that were accompanied by a $[Ca^{2+}]_i$ gradient (but not ICWs) in the direction of the injury site. The astrocyte polarization and Ca^{2+} response was proposed to guide microglial cells and was blocked by ATP and Cx channel blockers.

Panx1 channels have also been extensively studied as ATP releasing pores. They seem to play a key role in the release of this "find-me" signal from apoptotic cells for phagocytotic clearance [377,378]. Panx1 channels can be activated in cultured neurons and astrocytes, and in hippocampal slices, by elevated $[K^+]_e$, which can occur during different pathological conditions including epilepsy [379,380]. They have been proposed to mediate astrocytic ICWs via the release of ATP [94,181]. In leeches, nerve injury induces ICWs in glial cells and ATP release through channels composed of innexins, the invertebrate analogues of Cxs. Extracellular ATP then activates microglia and initiates microglial movement [256]. The injury site is also characterized by a delayed release of arachidonic acid, which blocks ATP release from glia after nerve injury and thereby stops microglia at lesions [381]. Panx1 has furthermore been implicated in the activation of the inflammasome, a multiprotein complex involved in innate immunity, in astrocytes and neurons [379]. Moreover, a number of studies have supported the idea that Panx channels are the pore-forming component of the $P2X_7$ receptor, with prolonged stimulation resulting in cell death [334,335,382]. Of note, from several studies it is also clear that extracellular ATP release not only mediates a rapid microglial response towards injury but it also regulates microglial branch dynamics in the intact healthy brain [374,383]. By imaging the visual center optic tectum in living larval zebrafish, Li and co-workers recently demonstrated a bi-directional regulation between resting microglia and neurons: a local increase in

neuronal activity results in the neuronal release of ATP via Panx1 channels, which attracts resting microglial processes and drives them to contact neurons with high levels of activity. The microglia–neuron contact in turn reduces the activity of contacted neurons [384].

5.5. Connexin-mediated communication, gap junctions versus hemichannels

Cx-mediated intercellular communication has been suggested to support the propagation of both pro-survival and pro-cell death messengers [291]. While treatments that suppress Cx43-based communication can re-inforce neurotoxicity in some models of neurodegenerative conditions [385,386], they may also be neuroprotective [318,319,387,388]. These opposite functions could relate to differences in the model systems used [291]. It should be noted that many of these observations were based on the use of non-specific channel blockers and/or genetic silencing of Cx expression, which affect both GJ and HC functioning. In addition, the genetic silencing of Cxs can modulate the expression levels of other proteins. It was recently demonstrated that the Cx43 and Cx30 deficiency in double KO mice differentially affects the expression of glial glutamate transporters depending on the brain region studied [389]. As such, more appropriate experimental tools are crucial to gain insight into the mechanisms via which Cxs affect cellular injury, e.g. by applying specific blockers that affect HCs or GJs only. Certain peptides derived from the Cx43 protein sequence can act as selective inhibitors of Cx channels [390–392]. Peptides targeting the *extra*cellular loops that inhibit HCs within minutes and GJs after several hours [393], are available for Cx26, Cx32, Cx37, Cx40 and Cx43 [392,394,395]. The Cx mimetic peptides Gap26 and Gap27, derived from the Cx43 sequence, have been used extensively to inhibit Cx channels in glial cells, giving rise to various effects such as inhibiting glutamate and ATP release, protecting neurons from excitotoxicity, inhibiting apoptosis and influencing neuroinflammation [86,267,331,344,396]. In addition, other peptides identical to sequences on the *intra*cellular parts of the Cx43 protein have been exploited to specifically inhibit HCs without influencing GJs [390,397,398]. Cx43 targeting peptides have been demonstrated to resort to beneficial effects in in vitro and in vivo models of CNS pathologies, including brain and retina ischemia [316,399,400], epilepsy [388,401], AD [402], optic neuropathy [403], spinal cord injury [319,404], and inflammation-induced BBB permeability [394].

5.6. Astroglial intercellular Ca^{2+} waves, a common factor in neurodegeneration?

The vast majority of research tackling the question of the Cx/Panx channel contribution to cell death has been performed in the context of the CNS. An increasing number of reports demonstrate a profound effect of pathological conditions on the expression of glial Cxs and Panxs, in particular Cx43 and Panx1, and their function as channels in a range of CNS diseases including epilepsy, traumatic brain and spinal cord injury, AD, and ischemia-related injury [405–410]. Below, we discuss the role of ICWs and Cx/Panx alterations in each of these disease states.

5.6.1. Brain ischemia

Cx-mediated intercellular communication may modulate the gradual expansion of cell death, as has been well-exemplified in the case of ischemia-induced injury. Although neurological cell death occurs within seconds to minutes after the ischemic insult in the core region, the progression of ischemic injury and cell death can continue for hours and days, thereby expanding the infarct region to the surrounding area termed the penumbra [411–414]. The latter is characterized by the presence of viable, yet metabolically compromised, cells that can be rescued by either restoring/improving perfusion or by counteracting neuronal damage. Many conceptually promising, therapeutic strategies based on targeting a variety of molecular cell injury/cell death pathways in neurons have failed in human studies, mainly because messengers causing destruction are also necessary for remodeling and repair afterwards [415]. Thus, specific messengers leading to cell injury need to be targeted at the right time before they adopt beneficial roles. Additionally, focus has shifted from the neurons towards the astrocytes, which are considered today as novel therapeutic targets [416–418]. Astrocytes are more resilient to ischemic injury compared to neurons, most likely due to their high levels of antioxidants and their prominent anaerobic energy metabolism [237,419]. However, once the astrocytic network fails, glutamate/K^+ clearance and energy delivery through the astrocyte–neuron lactate shuttle will stop and active release of neurotoxic mediators may start [235,236,239,420–422]. Hence, astrocyte-network distortion can critically contribute to neuronal death.

Cxs have been suggested to contribute to the wave of delayed secondary injury that spreads from the core region to the penumbra. Most studies emphasize a role for glial Cxs [408,423–426] but evidence for a contribution of neuronal GJs composed of Cx36 is accruing as well [42,427]. Ischemia-related injury is mostly associated with a reduction of astrocyte GJIC and an aberrant opening of Cx43 HCs [84,344,400,428,429]. However, despite the reduction in GJIC, there is evidence that a subset of GJs remains open and thus available for transferring cell death or survival signals under ischemic conditions [84,291,292,430]. Additionally, GJs may contribute to the propagation of cortical spreading depression (CSD), which consists of waves of tissue depolarization (20–80 μm/s) that have been linked to an increase in infarct volume after an ischemic insult [57,431–433]. CSD has been associated with slower propagating ICWs in astrocytes in vitro [190,434,435], and more recently also in vivo [247]. Here, CSD-associated ICWs first occurred in neurons but this was tightly coupled to a preceding ICW in astrocytes and to the vasoconstriction of intracortical arterioles [247]. The opening of Cx43 HCs will not only lead to astrocyte dysfunction and cell death by a collapse of membrane potential and the entry of Ca^{2+} [84,400,428,429], but will additionally allow the escape of glutamate and ATP that may further promote cell death [291,292,424].

Evidence for ICWs contributing to the expansion of brain infarction is also available. In response to photothrombosis-induced ischemia, cortical astrocytes in vivo showed large repetitive and transient Ca^{2+} signals within 20 min after photothrombosis which lasted up to 3 h [20]. They were synchronized and propagated as ICWs within the glial network, giving rise to Ca^{2+} signals in astrocytes in the penumbra. In contrast to neurons, astrocytes in the ischemic core retained their structural integrity for hours while an increase in reactive astrocytes was observed in the penumbra. Cortical loading of the Ca^{2+} buffer BAPTA into astrocytes significantly reduced the infarct volume. The astrocytic Ca^{2+} signals were triggered by mGluR5 and $GABA_B$ receptors [20]. A reduction of brain oxygen tension evokes increased frequency of spontaneous cerebellar ICWs in Bergmann glia in vivo, and $[Ca^{2+}]_i$ increases in Purkinje neurons [19]. Several authors have reported a role for astrocytic IP_3Rs in modulating ischemic damage. IICR is shown to be neuroprotective since the ischemic damage was aggravated in IP_3R2 KO mice which abolish astrocyte Ca^{2+} dynamics [218]. Finally, treatment with 2-aminoethoxydiphenyl borate, an inhibitor of IICR, decreased spontaneous Ca^{2+} oscillations in both astrocytes and neurons, and induced ischemic tolerance via a down-regulation of the glutamate transporter-1. A subsequent build-up of extracellular glutamate desensitizes the cells to the ischemia-induced glutamate increase [436]. An important issue to take into account is that 2-aminoethoxydiphenyl borate has off-target, inhibitory effects on Cx channels [437] and SOCs [438].

ICWs may be initiated by excessive neuronal firing or cell injury in the lesioned area. Once they are activated, they may self-sustain and expand $[Ca^{2+}]_i$ increases over larger populations, resulting in an expansion of the damaged area. However, as evidenced by a recent paper, astrocyte Ca^{2+} signaling is not necessarily a bad thing. In response to an ischemic insult, astrocytes in the contralateral hemisphere experience a boost in Ca^{2+} signaling which contributes to enhanced uptake of glutamate, thereby eliminating the excitotoxic trigger [439]. As contralateral astrocytes are not subject to energy deprivation this glutamate may be converted to glutamine and shuttled to starving

neurons. As such, astrocyte Ca^{2+} signaling might have different functions/consequences depending on the proximity of the lesioned area. Similar concepts may apply to other CNS diseases characterized by damaged core regions such as AD (Aβ plaques), brain trauma and epilepsy.

5.6.2. Alzheimer's disease

AD is considered as one of the most prevalent forms of dementia in humans. It is associated with several histopathological changes, including senile plaque formation, neurofibrillary tangles (NFTs), neuroinflammation, altered synaptic connectivity and ultimately irreversible, fatal neurodegeneration. NFTs are intraneuronal aggregates of paired helical filaments of abnormally hyperphosphorylated Tau protein. Senile plaques are extracellular aggregates mainly composed of Aβ surrounded by dystrophic neurites, activated microglia, and reactive astrocytes. AD mostly occurs as a late-onset, idiopathic or non-Mendelian form, while only about 5% is familial. Familial AD has an early onset and is inherited in an autosomal dominant manner due to mutations in the amyloid pathway such as in APP or PS1/2, which are the catalytic subunit of the γ-secretase complex that cleaves APP and releases Aβ.

The etiology of AD is poorly understood. The impairment of Ca^{2+} homeostasis is postulated to be an early event in the development of neurodegenerative processes [440]. Some suggest that altered Ca^{2+} signaling may decrease synaptic strength and cell loss well before initiating Aβ plaques while others place Aβ plaque formation as the start of Ca^{2+} deregulation [440,441]. The accumulation of NFTs and Aβ plaques may alter the Ca^{2+} household of the nervous tissue. For example, Tau proteins alter the function of voltage-gated Ca^{2+} channels [442] whereas PS form Ca^{2+} leak channels in the ER [443]. PS physically interact with SERCA, IP_3Rs and RyRs, facilitating ER Ca^{2+} uptake and release [283,444,445]. FAD-linked mutations in PS have been found to either abolish its Ca^{2+}-leak properties [443] or to result in a gain-of-function of IP_3R channels [283]. The latter seems to activate a vicious circle, further increasing the ratio of the toxic $Aβ_{42}$ over $Aβ_{40}$ levels. Interestingly, $Aβ_{42}$ can directly perturb intracellular Ca^{2+} homeostasis via IP_3R-dependent as well as -independent mechanisms [281]. Aβ also compromises the ability of neurons to restore $[Ca^{2+}]_i$ to baseline after a kainate and NMDA-induced elevation, making them more vulnerable to excitotoxicity [446]. In vivo evidence indicates that neurons in close proximity to Aβ plaques are hyperactive and experience a Ca^{2+} overload [261]. Importantly, Aβ-induced Ca^{2+} overload has not only been observed in neuronal cells but also in glial [262,447] and endothelial cells [448,449]. Especially glial cells have recently caught the attention of many leading AD research labs [450]. Atrophic and reactive astroglia were detected in AD mouse models [451], with reactive astrocytes being directly associated with Aβ plaques [451] and NFTs [452]. Activated astrocytes and microglia furthermore modulate senile plaque formation, either promoting [453] or inhibiting plaque growth [454]. Elevated $[Ca^{2+}]_i$ not only forms the basis for ER stress, glutathione depletion, ROS production and astrogliosis, but may furthermore stimulate the production and accumulation of Aβ peptide in astrocytes [262,263]. Mutations in PS have been shown to sensitize astrocytes to ATP and glutamate [289], and Aβ alters metabotropic Ca^{2+} signaling via a Ca^{2+}-calcineurin-nuclear factor of activated T-cells (NFAT)-dependent pathway. Aβ peptide activates calpain, which in turn cleaves and activates calcineurin, a vital component of NFAT-mediated gene expression. Both calcineurin and calpain are well acknowledged as Ca^{2+} oscillation sensors [455,456] and NFAT-dependent gene expression is thus tightly linked to $[Ca^{2+}]_i$ changes. Recent findings suggest that the Ca^{2+}-calcineurin-NFAT signaling axis is responsible for the overexpression of metabotropic GluR5, IP_3R1 and IP_3R2 in astrocytes surrounding Aβ plaques, resulting in altered Ca^{2+} homeostasis [290,457]. Importantly, Aβ differentially affects astrocyte metabotropic Ca^{2+} signaling in different brain regions which may account for the spatially distinct reactivity of astrocytes in the progression of AD [290].

Astrocyte ICWs have been shown to originate near Aβ plaques and spread 200 μm radially [21]. Based on the observation that photoactivation of caged IP_3 in astrocytes in vivo does not provoke ICWs, Crowe et al. [22] concluded that the spontaneous ICWs in AD mice do not depend on the IP_3-signaling axis. Increases in Cx43 and Cx30 expression have been observed in reactive astrocytes in the immediate vicinity of the majority of Aβ plaques in AD mouse models [313]. This is supported by an analysis performed in brain samples of AD patients, which displayed an increase in Cx43 expression [458]. Aβ reduces GJIC and induces HC opening in cultured astrocytes and brain slices [367,402], however, these observations are not supported by experimental results obtained from brain slices of APP-transgenic mice where GJ dye coupling through astrocytic networks was maintained in slices from different brain regions [459]. Interestingly, Aβ peptide has been shown to lead to neuronal death via a cascade of HC activation, composed of both Cxs and Panxs. First, activated microglia promote the release of glutamate and ATP through microglial Cx43 HCs and Panx1 channels and astrocytic Cx43 HCs, which subsequently induce neuronal death by triggering Cx36 HC and Panx1 channel opening in neurons [402].

5.6.3. Traumatic brain and spinal cord injury

Traumatic brain and spinal cord injury is often complicated by delayed progressively expanding cell damage and death to which Ca^{2+} ions and Cxs can contribute [460,461]. Several studies have demonstrated a neuroprotective role of Cx channel blockers/Cx silencing in traumatic CNS injury [42,319,387,404,462,463]. Not only neuronal Cx36 GJs play a role in the secondary neuronal death [463,464], but also Cx43 channels can increase neuronal vulnerability to brain or spinal cord injury [318,319,387]. Astrocytic Cx43 furthermore plays a role in the development of chronic neuropathic pain following spinal cord injury [320]. Cx43 expression and phosphorylation are upregulated in response to traumatic CNS injury [308,309,321,465–467] and the phosphorylation of Cx43 is associated with autophagy in hippocampal pyramidal neurons [467]. In addition, Cx29 and Cx32 expression are *de novo* expressed in astrocytes and microglia localized in the injury border zone [468].

Astrocyte ICWs were observed in vivo in the border/penumbral region after traumatic injury. These ICWs were dependent on purinergic signaling, and affected the neuronal activity and survival in the border zone [24]. ATP release via astrocytic Cx43 HCs is suggested to aggravate the secondary injury [318]. Inositol polyphosphates are also released from stretch-injured astrocytes in culture, suggesting that release of IP_3 from glial cells could affect neighboring neurons [469]. In accordance, HCs have been put forth as IP_3-releasing channels in the cochlea where the sensory neuroepithelium expresses IP_3R on the plasma membrane [77]. It must be noted that IP_3R expression has been identified in the plasma membrane of other cell types, but usually have the IP_3-sensing domain on the intracellular site [470]. It thus remains an open question whether such signaling route can be activated from outside the cell.

5.6.4. Epilepsy

Excessive neuronal firing during epileptic seizures is associated with marked alterations in the composition of the extracellular ions, most notably an increase in K^+ and a reduction of Ca^{2+} [471]. In accordance, lowering of $[Ca^{2+}]_e$, for example by stimulating glutamatergic synaptic transmission [254], has been shown to induce spontaneous epileptiform activity in hippocampal slices [472]. The resulting drop in extracellular Ca^{2+} stimulates CxHC opening that can further contribute to the translocation of Ca^{2+} ions to the intracellular compartment. Local or systemic administration of IP3-linked metabotropic glutamate receptor agonists can further contribute to excessive neuronal firing. Antagonists of these receptors indeed have anti-convulsant properties. Additionally, several anti-epileptic agents reduce the ability of astrocytes to transmit Ca^{2+} signaling [26].

Astrocytes isolated from human epilepsy patients display an increase in GJIC, and a surge in glutamate-induced Ca^{2+} oscillations and ICWs [473], which might be the consequence of an elevation in extracellular K^+ concentration ($[K^+]_e$) [474]. The contribution of Cx channels to ictogenesis is dual [4]. On the one hand, GJs may be anti-convulsive by contributing to spatial buffering of K^+ and glutamate. The combined ablation of Cx43 and Cx30, which results in coupling-deficient astrocytes, lowers the threshold for epileptiform activity and thus supports this notion [52,57]. On the other hand, GJIC may be pro-convulsive by helping to provide neurons with the energy supply required for neuronal bursting, while ICWs propagated by GJs and CxHCs may expand the hyperexcited Ca^{2+} state of the astrocyte network thus modulating remotely located synapses [44,49]. In this respect, pharmacologic block of Cx channels reduced seizure activity while a potentiation of cell–cell coupling enhanced neuronal firing [52,388,475]. Interestingly, recent evidence based on work with a peptide targeting the second extracellular loop of Cx43 indicates that during an epileptiform insult, Cx43 HC opening is detrimental while GJIC is neuroprotective. By contrast, after the seizure, GJIC exacerbates neuronal death [388].

Astrocytes themselves may be the origin of glutamate in epileptic firing. Tian and co-workers [26] reported that paroxysomal depolarization shifts (PDSs, abnormally prolonged depolarizations with repetitive spiking manisfesting as interictal discharges) can be initiated by the release of glutamate from extrasynaptic sources. The application of the K^+ channel blocker 4-aminopyridine in the somatosensory cortex in vivo triggered PDSs, and stimulated the appearance of astrocytic ICWs and repetitive oscillatory Ca^{2+} increases. Astrocytic Ca^{2+} signaling invariably preceded bursting activity and flash photolysis of caged Ca^{2+} in astrocytes was sufficient to trigger PDSs. Additional support for an astrocytic origin is provided by the observation that intracellular dialysis of IP_3 into single astrocytes evokes glutamate release and epileptiform discharges in adjacent neurons in hippocampal slices [476]. Two later studies demonstrated that glutamate release from astrocytes is not necessary to evoke epileptiform activity in hippocampal slices [477], but can evoke neuronal cell death in an in vivo model of status epilepticus [25].

6. Conclusions

For decades, research has been focusing on the neuronal abnormalities that accompany neurodegenerative disorders. However, at the same time, it is becoming increasingly evident that astrocytes are also important players in various CNS diseases. Reactive glial cells (mainly astrocytes and microglia) have been identified in many disorders of the CNS which boosted the interest in the potential role of these cells in neuronal injury. Astrocytes form extensive networks that connect neuronal synapses with the vasculature. This central position provides astrocytes with several essential functions, i.e. sensing neuronal activity as well as participating in their signaling, integrating electrochemical information and exchanging this information with the vasculature. Hereby, the canonical PLC/IP_3/Ca^{2+} pathway is the language via which astrocytes talk to each other as well as to neurons, microglia and vascular cells. The information processing within the glial network, as well as the communication of this information to NGVU partner cells is supported by intercellular signaling via GJs or via paracrine communication, possibly involving HCs. As such, it is no surprise that alterations of Cx channel function will profoundly affect proper functioning of the NGVU and will ultimately lead to cell dysfunction and cell death. An increasing number of publications have reported the occurrence of glial ICWs in vivo in various acute and chronic animal disease models such as epilepsy, ischemia, brain trauma and AD. The exact functional implications of these glial-based ICWs are unclear. As suggested here, they might provide the long-range transfer of information to evoke processes such as reactive astrogliosis, microglial activation and neurodegeneration. A balance between these processes likely determines the overall influence exerted by astrocytes in these conditions, saver versus killer, and the level of destruction, protection and regeneration in neuropathological conditions. These examples of pathological conditions suggest further research to explore the terms and mechanisms leading to increased appearance of ICWs, and to determine their contribution in the pathogenesis and disease progression. Research on Cx-mediated Ca^{2+} communication within the NGVU may ultimately shed light on the development of targeted therapies for gliopathologies.

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